Lisa D Rarick, MD
RAR Consulting, LLC
Reproductive Health and Regulatory Affairs
215 Midsummer Circle
Gaithersburg, MD 20878
301.548.9750
rarick215@comcast.net

Written Testimony/Prepared Statement re:
"RU-486: Demonstrating a Low Standard for Women's Health?"
Subcommittee on Criminal Justice, Drug Policy and Human Resources
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Good afternoon and thank you, Mr. Chairman and members of the subcommittee, for the opportunity to provide testimony in this important discussion of the use of mifepristone for medical abortion.

My name is Lisa Rarick. I am a medical doctor with training and board certification in Obstetrics and Gynecology. I received my medical degree from Loma Linda University School of Medicine in 1984 and my Ob/Gyn training at Georgetown University 1984-88. After my residency, I remained on the faculty of the Department of Ob/Gyn at Georgetown and soon also began to work at the US Food and Drug Administration (FDA).

Although my work at the FDA began as a part time position in the Center for Drug Evaluation and Research (CDER) looking into fetal effects of drug exposure (Accutane and seizure medications were the main focus of this work in the late 1980's), I quickly grew interested in CDER's broader mission of protecting and promoting public health through pharmaceutical regulation.

I transitioned to part-time clinical practice and full time employment at the FDA by September of 1989. By 1993 I was no longer involved in individual patient care. I maintain my medical license with both the State of Maryland and the District of Columbia and my Ob/Gyn board certification through the American Board of Obstetrics and Gynecology.

My work at CDER progressed from the review and analysis of fetal exposure information to work as a primary medical reviewer (also called Medical Officer) for new drugs in the Division of Metabolic and Endocrine Drug Products. As a Medical Officer I had responsibility for the review of investigational and approved drugs used in various conditions for women's health.

In 1996 a new Division (the Division of Reproductive and Urologic Drug Products) was created. I was named as its first Division Director and remained in that position for the next 3.5 years (June 1996-Dec 1999). During that time I was well acquainted with the application for mifepristone and participated in the review as well as the Advisory Committee meeting discussions regarding this product. I was actively involved in the regulatory actions taken for this product during my tenure as Division Director. In December, 1999 I moved up CDER's

organizational ladder from Division to Office level and became the Deputy Office Director for the Office of Drug Evaluation 2. This Office did not have responsibility for the mifepristone application. After a year at the Office level I took a position with the Center Director's Office (under the direction of Dr. Janet Woodcock) as the Associate Director for Quality Assurance. Among other things, this office was charged with implementing "good review practices" across the entirety of the Center for Drug Evaluation and Research.

I spent my final year at the FDA (July 2002-July 2003) in the Office of Women's Health in the Office of the Commissioner under the directorship of Dr. Susan Wood. Since leaving government service in the summer of 2003 I have provided consulting services to pharmaceutical companies, venture capital, advocacy groups and individuals regarding regulatory affairs and reproductive health.

My conclusions after review of the available scientific information regarding mifepristone while at the Agency as well as my subsequent review are consistent with the FDA's conclusions. The approval of mifepristone in September, 2000 was based on more than the necessary number of studies submitted and reviewed by the division of which I was director. As many are aware, an application submitted to the FDA to support a new drug approval must contain adequate and well-controlled studies to confirm efficacy and safety. Generally the word "studies" is interpreted as requiring two adequate studies. Although there are some instances where one study is acceptable,[1] most applications contain the usual two confirmatory clinical trials. In the case of mifepristone, three studies were submitted in order to establish efficacy and safety for early intrauterine pregnancy termination.

The clinical review included analyses of all human studies utilizing mifepristone including these three Phase 3 studies involving close to 2500 women. The Reproductive Health Drugs Advisory Committee was convened and asked to discuss and provide recommendations during the review of this application. The Committee reviewed the two Phase 3 studies conducted in France as well as preliminary US clinical study information in 1996. They also heard from over 30 speakers during the Open Public Hearing portion of that meeting. They recommended by a vote of 6-0 (with 2 abstentions) that benefits exceeded risk.

The approval action taken by the Agency in September, 2000 utilized the regulatory option of "subpart H" restrictions for this product. Contrary to the assertion that the subpart H designation was based on a desire for "accelerated" approval of mifepristone, this is clearly not the case. The application for marketing of mifepristone was submitted in March, 1996 and approved in September of 2000. Certainly FDA, pharmaceutical companies and other interested parties can agree that a review and approval process of 4 plus years does not meet any regulatory definition of "fast" or "accelerated". In this case, the application of subpart H regulations actually provided FDA with more rigorous oversight and allowed for the formal imposition of restricted distribution. As per the regulation (21 CFR 314.500-314.560), one application of the subpart H regulations allows for approval in situations "when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted". Subpart H approval also allows for more oversight of promotional materials and a streamlined

[1] Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" May 1998

mechanism for withdrawal procedures. In essence, the subpart H approval was meant to restrict the use of mifepristone, not "accelerate" its availability.

Clearly, since approval, the FDA has remained extremely vigilant in its regulatory oversight of mifepristone. The labeling has been revised three times since its year 2000 approval. Each of these labeling change actions followed a complete FDA review of the clinical studies and postmarketing information available for mifepristone and resulted in updated presentations of scientific information for consideration by prescribers and patients. Labeling revisions such as these are an important and expected part of drug regulation and indicate active and appropriate review of post-approval information.

As with any medication, when reports of serious adverse events associated with mifepristone use are received by FDA, they are carefully analyzed and rigorous investigation is employed to ascertain the relationship, if any, between the drug and the event, as well as to ascertain mechanisms to prevent similar events in the future. I applaud the efforts of the FDA to better understand the recent findings of serious bacterial infection reported in a small number of women after mifepristone use and in other pregnancy-related conditions.

In particular, as you know, the FDA, Centers for Disease Control and Prevention (CDC) and the National Institutes of Health-National Institute of Allergy and Infectious Disease (NIH-NIAID) held a joint meeting on May 11 of this year. This meeting was an effort in which experts came together to better understand reports of morbidity and mortality associated with clostridial infections. My understanding from those who attended the meeting is that the rare cases of clostridial infection and death reported in mifepristone users are, at this time, not explained by a simple drug-based association. In fact, the presentations and discussion made it clear that these infections are occurring in various pregnancy-related conditions, not only post-abortion settings. I say this not to dismiss the fact that some infections are occurring in women who have chosen medical abortion, but to emphasize that the agencies must—and are—looking at the infection trends more broadly. Further investigation and understanding of these infections in various pregnancy-related outcomes is essential. Although we in the scientific community must be open to all possibilities—and I believe we are—to date no evidence has emerged to support the hypothesis that mifepristone interferes with the immune response and thus allows for widespread multi-organ infection in women. Immune suppression-associated infection in this setting would not appear as reports of the appearance of one organism, but would present as infections with any or all of the various bacteria present in the female reproductive tract. In addition, this infection has not been reported in patients with known immune suppression such as those with HIV, cancer, or those who are on immunosuppressive drug regimens. Again, we should not close off consideration of any serious hypothesis, but to date the hypothesis that mifepristone itself is a cause of these infections is not supported by the data.

As I mentioned earlier, the FDA is actively investigating reports of death and serious adverse reactions with mifepristone. CDER is charged with a mission to protect and promote the public health through regulation of pharmaceuticals. The medical review team for mifepristone (both pre- and post-approval) was and is clearly aware of the science and results assessing both risks and effectiveness of the use of mifepristone for the medical termination of early intrauterine

pregnancy. In other words, the system is working; investigation is underway, I urge Congress to allow the agencies to continue their work.

I would also like to say a word about medications and risk, generally. As for any medical procedure or treatment, the review and analysis of medical abortion must be seen in the context of approved alternatives. For many diagnoses multiple options exist for treatment—each with differing risk profiles. For example, in the arena of women's health—endometriosis and fibroids, while once conditions treated primarily through surgical means, now have approved pharmaceutical treatment options. Men were once faced with only device and surgical options for management of erectile dysfunction. I believe we are all aware that medical options now exist. Prostate, cervical cancer and breast cancer patients are faced with decisions of benefits and risks regarding options of surgery, medication, radiation and sometimes combination treatments or other modalities. All of these various methods for treatment offer different risk/benefit considerations. One modality is not considered "best" for any specific condition, but all modalities must be considered and applied to the individual case decision.

Women and couples are faced with complex decisions when it comes to pregnancy termination—not only terminations in the context of unintended pregnancies, but also in the case of non-viable pregnancies and in the management of spontaneous abortion ("miscarriage"). Clearly mifepristone offers a safe alternative to surgical abortion. Every option available to pregnant women presents different risks and benefits. Medical abortion is one option for those who choose or require early pregnancy termination. FDA clearly believes, as I do, that women and their providers must be well-informed regarding risks of medical abortion. This belief is based on the principle of informed consent, which states that before any medical care is delivered, the patient must be informed about the risks, benefits, and alternatives, and understanding those facts, must give consent. I believe informed consent for mifepristone is being adequately provided through the process the FDA imposed on the medication with its approval. Specifically, the approval of mifepristone included mandated FDA-approved prescribing information, FDA-approved Medguide,[2] and a patient agreement form. In my experience, these restrictions on a medication are unusual and, in my view, are one indication of many that the FDA is taking its oversight responsibilities seriously.

In conclusion, I urge this subcommittee to allow the FDA to continue to do its job. There is no evidence that FDA is shying away from the difficult questions of risk and benefit for this indication. Risks are being investigated. Adverse event reporting for medical abortion is uncovering and forcing investigation of previously unexplored risks related to pregnancy and post-pregnancy events. Let us all continue to support FDA and others as they fulfill their mission to protect and promote the public health. The public can only have confidence in the FDA's conclusions if it knows it is impervious to political pressure. I urge us to resist the temptation to interfere in this instance, and instead for Congress to allow the dedicated public health professionals at the FDA to do their jobs, continue their investigation, and take any actions that might be needed to protect and promote women's health.

[2] 21 CFR 208 "Medication Guides for Prescription Drug Products"